UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/344,189	06/24/1999	CHARLES E. ROGLER	0342/1D888US	8764

7590 11/23/2001

DARBY & DARBY
ANNE E ZITRON PH D
805 THIRD AVENUE
NEW YORK, NY 10022

EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/344,189	ROGLER, CHARLES E.	
	Examiner	Art Unit	
	Peter Paras	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's amendment filed on September 7, 2001 has been entered. Claims 1, 8, 14, 23, 25, and 35 have been amended. New claims 37-38 have been added. Claims 1-38 are pending and are currently under consideration.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 as originally filed, amended or newly added are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a chimeric, immunodeficient (SCID) mouse, lacking mature B and T cells and having a degenerated liver parenchyma which is repopulated with transplanted mammalian hepatocytes that are infected with a compatible hepatitis virus, wherein the somatic and germ cells of the mouse comprise a transgene encoding a urokinase-type plasminogen activator (uPA) operably linked to albumin promoter, and wherein expression of the transgene results in liver degeneration; and methods of using the same mouse does not reasonably provide enablement for a method of making any chimeric, immunetolerant mouse having a degenerated liver and comprising xenogenic mammalian hepatocytes which can be infected with a compatible hepatitis virus; and methods of using the same chimeric, immunetolerant mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these

claims. The prior rejection is maintained with respect to the immunetolerant mouse, liver degeneration, and hepatocellular carcinoma development for the reasons of record advanced in the Office action mailed on 6/7/01 on pages 3-11.

The aspect of the enablement rejection with regard to infectivity of xenogenic hepatocytes with hepatitis viruses as set forth in the first full paragraph on page 7 and the paragraph bridging pages 7-8 is withdrawn. Applicant's arguments to that end are moot.

The aspect of the enablement rejection with regard to the uPA homozygous transgenic mice as set forth on pages 6-7 of the Office action mailed on 6/7/01 is withdrawn. Applicant's arguments to that end are moot.

Applicant's arguments have been fully considered but they are not persuasive. Applicants have argued that the claims as amended are now directed to an "immunetolerant mouse deficient in T and B cells". Applicants assert that none of the mice disclosed in Baumgardner are deficient in both B and T cells. See pages 5-7 of the amendment.

In response, the Examiner asserts that only mice that lack or are devoid of functional B and T cells are enabled as recipients of xenogenic hepatocytes. The amended claims are now directed to an "immunetolerant mouse deficient in T and B cells". However, the term "deficient" does not equate with lacking or devoid of, as an "immunetolerant mouse deficient in T and B cells" may still contain some functional T and B cells that may lead to graft rejection given the definition of the term "deficient". The Random House College Dictionary has defined the term "deficient" as follows:

insufficient or inadequate. Such a definition leaves room for interpretation as to the existence of any functional T and B cells in the claimed mouse. In light of such, it is maintained that the state of the art suggests that mice having a SCID phenotype, devoid of functional of T and B cells, are superior acceptors of xenogenic tissue transplants. See the Office action mailed on 6/7/01 on pages 4-5. Baumgardner et al provide support for such an observation by demonstrating the only mice having the SCID phenotype do not reject transplanted hepatocytes. See pages 4-5 of the Office action mailed on 6/7/01. Amending the claims to recite an immunetolerant mouse "lacking" or "devoid of" functional T and B cells may be sufficient to overcome this aspect of the enablement rejection.

Applicants have argued that methods other than expression of the uPA transgene for creating a degenerated liver were known in the art, contrary to the Examiner's position. Applicants have relied on Laconi and Overturf for support. See pages 7-9 of the amendment.

In response, the Examiner maintains that the instant specification does not support other methods for creating a degenerated liver. See page 6 of the Office action mailed on 6/7/01. In fact, the instant specification does not mention use of chemicals or other specific transgenes for creating a degenerated liver; the instant specification only prophetically alleges that "other" methods for creating a degenerated liver may be employed. As such relevant teachings or guidance for the creation of a degenerated liver are lacking in the instant specification. The working examples exemplified by the instant specification are directed only to hemizygous or homozygous uPA transgenic

mice. The references, Laconi and Overturf, relied on by Applicants to support assertions that other methods may be used for creating a degenerated liver which can support xenogenic hepatocytes are not persuasive to that end. Neither Laconi nor Overturf teaches the use of xenogenic hepatocytes; both references teach engraftment of hepatocytes of the same species into their respective animal models. There is no teaching or suggestion in either reference that their respective models may support xenogenic mammalian hepatocytes. In fact as the animals of Laconi and Overturf appear to have normal immune systems it would be unpredictable for such to support xenogenic hepatocytes. Finally, neither Laconi nor Overturf teach or otherwise suggest use of their respective methods on mammals lacking B and T cells for the purpose of grafting xenogenic hepatocytes.

Applicants argue that one of ordinary skill in the art could readily determine the combination of transplanted xenogenic hepatocyte and compatible hepatitis virus to practice claims 25-36. Applicants assert only H & E stained liver sections are necessary to identify precancerous altered hepatic foci.

In response, the Examiner maintains that not all hepatitis viruses cause hepatocellular carcinoma (HCC). See Fields Virology on page 8 of the Office action mailed on 6/7/01. The claims as written do not require development of HCC prior to administration of the potential anti-cancer agent. As infections from some of the mammalian hepatitis viruses do not result in HCC it is unclear how potential anti-cancer agents may be screened by administration prior to onset of HCC. Furthermore, although there appears to be a correlation between HCC and hepadnavirus infection,

not all hepadnavirus infections result in HCC. See Fields Virology, pages 1006-1010. In light of such, the claims as written do not appear to be operable for screening of potential anti-cancer agents.

Accordingly, the standing aspects of the prior enablement rejection are maintained for the reasons of record.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejections of claims 1-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-5, 8-12, 15-21, 25-33, and 36-38 as originally filed, amended, or newly added are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al. The prior

rejection is maintained for the reasons of record advanced on pages 13-14 of the Office action mailed on 6/7/01.

Applicants have argued that Kay et al does not teach each and every embodiment of the instant claims. Applicants assert that the disclosure of Kay et al fails to enable one of ordinary skill in the art to make the disclosed animal. Applicants further argue that Kay et al does not offer any direct guidance as to the procedures to be used in the allegedly disclosed method for transplanting human hepatocytes into the degenerated liver of an immunetolerant mouse.

In response, the Examiner maintains that the disclosure of Kay et al teaches all the embodiments of the claimed invention. Contrary to Applicant's position, the Examiner asserts that the methods of Kay et al enable one of ordinary skill to create the claimed chimeric mouse. First, Kay et al teach that expression of the uPA transgene in the liver of a transgenic mouse results in liver degeneration, wherein the degenerated liver may be repopulated with hepatocytes that do not express uPA. See columns 2-3. Kay et al go on to teach that xenogenic hepatocytes, particularly human, may be used to repopulate the degenerated liver when the uPA transgene is expressed in a mouse having a SCID background. See columns 3 and 8, particularly lines 11-15 of column 8. The alb-uPA mouse, having a degenerated liver phenotype, at the time of filing of Kay et al was known in the art and was readily available to the ordinary artisan as evidenced by the disclosure of Kay et al. In light of such it was known what level or what period of time the uPA transgene need be expressed to cause liver degeneration. See columns 2-3. Kay et al teach a transgene encoding a modified uPA that is not secreted by

hepatocytes into the bloodstream, but otherwise functions the same as wild-type uPA. See column 5. In any event, Kay et al teach that a transgenic mouse, comprising and expressing a modified uPA transgene, having a SCID background may be used as a recipient for xenogenic hepatocytes, wherein expression of uPA results in liver degeneration, and wherein said xenogenic hepatocytes have repopulated said degenerated liver and are infected with a hepatitis virus such that said xenogenic hepatocytes serve as a model for hepatitis infection and its treatment. See column 7 beginning on line 51 bridging to column 8 through line 18.

Contrary to Applicant's assertions of the last paragraph of page 15, the disclosure of Kay et al does teach that liver degeneration is effected by genetic transmission of a uPA transgene. See Kay in columns 2-3. The Examiner agrees with Applicants that Kay et al does not teach a uPA/RAG-2 chimeric mouse comprising woodchuck hepatocytes, wherein the woodchuck hepatocytes are infected with woodchuck hepatitis virus or methods of producing the same mouse; such limitations may be considered allowable over Kay et al.

In view of the preceding paragraphs and the reasons of record the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejections of claims 1-5, 8-9, and 11-12 under 35 U.S.C. 103(a) as being unpatentable over Rhim et al taken with Vierling et al, claims 6, 10, and 13 as being obvious over Rhim et al taken with Vierling et al and further in view of Alt et al, and claims 7 and 14-36 as being obvious over Rhim, Vierling, and Alt and further in view of Roggendorf et al are withdrawn in view of the Rogler declaration.

The following are new grounds of rejection under 35 U.S.C. 103(a):

Claims 1-6, 8-13, 15-22, 24-34, and 36-38 as originally filed, amended, or newly added are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al taken with Alt et al.

The claims are directed to a chimeric, immunodeficient (SCID) mouse model, particularly a homozygous uPA/RAG-2 knockout transgenic mouse, wherein xenogenic mammalian hepatocytes, are transplanted into the liver parenchyma of the mouse and infected with the appropriate species-specific hepatitis virus. The claims are also directed to methods of making the same mouse. The claims are further directed methods of using the same mouse for screening potential antiviral and anticancer compounds.

Kay et al teach that a transgenic mouse expressing a uPA transgene has a phenotype of liver degeneration, wherein the liver of said mouse can be repopulated with non-native hepatocytes; such a mouse was readily available to the ordinary artisan.

See columns 2-3. Kay et al teach that such a uPA transgenic mouse may be bred with a SCID mouse so that the degenerated liver may be repopulated with human hepatocytes, that can be infected with a hepatitis virus. Kay et al teach that such a mouse can be used as a model of hepatitis infection, particularly hepatitis A, B, and C. See columns 7-8. Kay et al also teach that ribozymes, hormones, cytokines, enzymes, antigens, antibodies, clotting factors, anti-sense RNA, regulatory proteins, fusion proteins and the like, may be used for treating a disease [particularly hepatitis, hepatocellular carcinoma that results from chronic hepatitis B or C infection] in the same chimeric mouse model. Particularly Kay et al teach that ribozymes may be used to inhibit HCV replication, which can be assayed by quantitative RT-PCR.

However at the time the claimed invention was made, it was well known to the ordinary artisan that RAG-2 deficient mice have an improved SCID phenotype. Alt et al teach a severe combined immunodeficient (SCID) mouse that resulted from homozygous disrupted recombination activating gene (RAG) 2. Disruption of the RAG-2 genes results in a novel SCID phenotype. See column 2. Alt et al discuss that SCID mutated mice comprising altered VDJ recombinase genes can have a leaky phenotype resulting in production of B and T lymphocytes that can result in rejection of implanted tumor cells. RAG-2 deficient mice have an improved SCID phenotype that is not leaky. Alt et al further discuss that human tissue such as tumor cells, lymphoid progenitors, fetal liver cells may be implanted in RAG-2 deficient mice to create chimeric mice (see columns 3-4) and that such a mouse provides for methods of identifying and evaluating drugs, and evaluating different therapeutic protocols against infections, viral infections,

and tumors (see column 6). Alt et al specifically discuss that the viral infection may be a hepatitis virus infection and suggest that infection of hepatocytes make occur following implantation (see column 6).

Accordingly, in view of the teachings of Alt et al it would have been obvious at the time the claimed invention was made to modify the teachings of Kay et al by breeding a RAG-2 knockout mouse with a uPA homozygous transgenic mouse to create a RAG-2/uPA homozygous mouse that can be a recipient for transplanted xenogenic hepatocytes. One of ordinary skill would have been sufficiently motivated to make such a modification because a RAG-2 homozygous knockout mouse represents a novel, improved SCID phenotype that does not result in transplant rejection because a RAG-2 homozygous knockout mouse has a phenotype that does not result in leaky production of B and T lymphocytes as taught by Alt and more particularly because Alt has suggested that RAG-2 knockout mice may be used as recipients for transplanted liver cells and as models for testing antiviral therapies, such as hepatitis virus therapy.

Thus, the claimed invention as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 7, 14, 23, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al taken with Alt et al as applied to claims 1-6, 8-13, 15-22, 24-34, and 36-38 above and further in view of Roggendorf et al.

The claims are directed to the same invention as described above, particularly when the xenogenic hepatocytes are woodchuck and the hepatitis virus is woodchuck hepatitis virus.

Kay et al teach that a transgenic mouse expressing a uPA transgene has a phenotype of liver degeneration, wherein the liver of said mouse can be repopulated with non-native hepatocytes; such a mouse was readily available to the ordinary artisan. See columns 2-3. Kay et al teach that such a uPA transgenic mouse may be bred with a SCID mouse so that the degenerated liver may be repopulated with human hepatocytes, that can be infected with a hepatitis virus. Kay et al teach that such a mouse can be used as a model of hepatitis infection, particularly hepatitis A, B, and C. See columns 7-8. Kay et al also teach that ribozymes, hormones, cytokines, enzymes, antigens, antibodies, clotting factors, anti-sense RNA, regulatory proteins, fusion proteins and the like, may be used for treating a disease [particularly hepatitis, hepatocellular carcinoma that results from chronic hepatitis B or C infection] in the same chimeric mouse model. Particularly Kay et al teach that ribozymes may be used to inhibit HCV replication, which can be assayed by quantitative RT-PCR.

However at the time the claimed invention was made, it was well known to the ordinary artisan that RAG-2 deficient mice have an improved SCID phenotype. Alt et al teach a severe combined immunodeficient (SCID) mouse that resulted from homozygous disrupted recombination activating gene (RAG) 2. Disruption of the RAG-2 genes results in a novel SCID phenotype. See column 2. Alt et al discuss that SCID mutated mice comprising altered VDJ recombinase genes can have a leaky phenotype

resulting in production of B and T lymphocytes that can result in rejection of implanted tumor cells. RAG-2 deficient mice have an improved SCID phenotype that is not leaky. Alt et al further discuss that human tissue such as tumor cells, lymphoid progenitors, fetal liver cells may be implanted in RAG-2 deficient mice to create chimeric mice (see columns 3-4) and that such a mouse provides for methods of identifying and evaluating drugs, and evaluating different therapeutic protocols against infections, viral infections, and tumors (see column 6). Alt et al specifically discuss that the viral infection may be a hepatitis virus infection and suggest that infection of hepatocytes make occur following implantation (see column 6).

The collective teachings of Kay et al and Alt et al do not teach the use of woodchuck hepatocytes or woodchuck hepatitis virus for use in the immunetolerant uPA transgenic mouse.

However at the time the claimed invention was made, Roggendorf et al teach that the woodchuck and the woodchuck hepatitis virus (WHV) have been studied and used as the most suitable model for human hepatitis B virus infection. WHV is closed related to the human virus, having strong similarities in morphology, genome structure and gene products, replication, epidemiology, the course of infection and in the development of illness and hepatocellular carcinoma (HCC). In particular the woodchuck is currently used to study pathogenesis of hepadnavirus infection, molecular mechanisms of HCC development, and cell tropism of hepadnaviruses; also woodchucks are used to study different approaches for new vaccines to hepadnaviruses and evaluation of antiviral drugs in chronic WHV infection. See page

100 and abstract. Roggendorf et al discuss that chronic WHV infection almost inevitably develops into HCC. See page 104. Roggendorf et al discuss specifically *in vivo* testing of antiviral drugs, including immune modulators, in the woodchuck model of hepatitis, particularly chronic hepatitis infection; nucleoside analogs in particular are discussed as antiviral agents (and also as anticancer agents as treatment of chronic WHV infection would also treat HCC because chronic WHV results in HCC). See pages 108-109.

Accordingly, in view of the teachings of Roggendorf et al, at the time the claimed invention was made, it would have been obvious for one of ordinary skill in the art to modify the teachings of Kay et al and Alt et al by creating a chimeric uPA/RAG-2 knockout homozygous mouse comprising woodchuck hepatocytes, wherein such a chimeric mouse can be used as a model for WHV infection as well as for testing potential antiviral and anticancer compounds for the prevention of WHV replication and HCC development. One of ordinary skill would have been sufficiently motivated to make such modifications as it was an art-recognized goal to create animal models of hepatitis infection that relate to human hepatitis infection for testing of antiviral and anticancer compounds as taught by Roggendorf et al, particularly as Roggendorf has suggested that the woodchuck and WHV may be the most suitable model for human hepatitis B virus infection and as Kay et al has suggested that non-native hepatocytes may be used to repopulate the degenerated liver of an immunetolerant uPA transgenic mouse.

Thus, the claimed invention as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

Art Unit 1632

Deborah Clark

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600